Simple on the Surface, Complex Underneath: Lessons from a Real-World Trial

By Sony Salzman

Trying to make a real-world data study as easy as possible for practitioners and participants requires a great deal of work behind the scenes, experts say, but careful planning pays off.

Representatives of GlaxoSmithKline’s Salford Lung Study (SLS) say there are unique challenges in conducting a trial that brings together both clinical research and real-world data.

The benefit of such hybrid studies is their ability to answer questions about a therapy’s safety and efficacy while simultaneously collecting information about the best way to implement that therapy in a real-world setting.

The SLS, the first major drug trial conducted under “real world” conditions, evaluated GSK’s Relvar among 4,233 patients with asthma and 2,802 patients with chronic obstructive pulmonary disease (COPD). The studies were designed as open-label, Phase 3, randomized trials.

The goal of the trial was to show the benefit of a once-daily administered drug, says Elaine Irving, senior director and head of real-world study delivery at GSK, which can’t be done in a blinded scenario. GSK focused the trial on practical endpoints that physicians use in day-to-day practice, Irving says, and tried to keep the patients as close to routine care as possible. Active randomization helped maintain scientific rigor.

The first lesson learned, Irving points out, was how many moving parts such a study requires. A second overwhelming obstacle was getting, copying and printing.

Lessons from a Real-World Trial

Easy Document Access Key to Inspection Success, Expert Says

By Leslie Ramsey

When the FDA shows up with inspection notice in hand, will you be able to produce the documents they request quickly and efficiently? Knowing where all your records are stored and what condition they are in is vital to inspection success, says one former FDA district director.

Even though “clinical trial monitoring records are sort of like ‘mini audits,’” says quality consultant and 23-year FDA veteran David Chesney, sites still are subject to FDA inspection.

Chesney offers several tips for making sure records the FDA wants to see are labeled, stored, archived and easily accessible during an inspection.

Start with a consistent naming convention that is unique but succinct. File names in electronic systems often are cut short, so document titles should be identifiable by only a few words or numeric designation. And whatever convention you use, train the staff that will retrieve documents to recognize them quickly.

Archived documents should be held in easily accessed locations or designated drives, in the case of electronic records, which also should have controls over reading, copying and printing.

Inventory documents by owner, Chesney advises, and periodically reconcile that inventory to make sure documents are present. And develop both a written retrieval plan and the ability to answer questions about a therapy’s safety and efficacy while simultaneously collecting information about the best way to implement that therapy in a real-world setting.

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Sharpless Says Innovative Trial Designs Are FDA Priority

Innovative trial designs are a high priority in FDA plans, acting FDA Commissioner Ned Sharpless said in an agency-wide internal email sent Tuesday.

Sharpless told staffers the agency will continue to push for the use of platform trials, basket studies, adaptive trials and pragmatic randomized controlled trials that will save money and time on research and development. It also plans to promote the use of real-world evidence (RWE) in both pre- and postmarket adverse event detection and efficacy analyses in clinical situations that may not be able to use randomized trials.

“Enhanced use of RWE for regulatory decisionmaking will improve the generalizability of evidence to patient populations that may be excluded from traditional clinical trials,” he added.

The agency will continue to use novel approval pathways for drugs, biologics and devices — including RMAT, Accelerated Approval and Breakthrough — as they can make product development more efficient, Sharpless said.

Big Pharma Scores Well Overall on Data Transparency

Roche/Genentech and Novo Nordisk tied for top honors for data transparency on Bioethics International’s latest Good Pharma Scorecard.

The two companies both scored 100 percent on the nonprofit’s annual evaluation of big pharma’s track record on trial registration, results reporting, publication and data-sharing practices. Novartis was close behind at 99 percent.

The median score of the 12 companies evaluated – based on their sharing of data on 2015 FDA-approved drugs – was a respectable 92 percent, according to the study, but three companies fell below the 70 percent mark: Valeant at 63 percent, Amgen at 56 percent and Allergan, soon to be absorbed by AbbVie, at the bottom of the list with a poor transparency score of 46 percent.


EMA Studies Patient Registries’ Use in Rare Disease Trials and Postmarket Surveillance

Patient registries could provide valuable data for regulatory decisions, a new EMA drug safety study indicates.

Registries can be used when randomized controlled trials are not feasible, such as in the case of some rare diseases, or to meet postmarketing commitments.

The study further explains how registries are currently underused and explained how the absence or incompleteness of ten different factors impeded registry use. Factors include the use of common core data sets, common data coding terminologies, data access and sharing and data linkage capacity, among others.

“From a regulatory perspective, the ultimate requirement of patient registries is that they permit the conduct of high quality studies that evaluate the safety and effectiveness of medicines,” EMA says.

The agency plans to prepare a preliminary discussion paper and solicit public comments before issuing methodological and operational guidance on handling registry data in postmarket studies.

Industry, Academia Form Consortium to Develop Neurobehavioral Clinical Tools

Several big pharma companies have joined with European universities and an AI technology company to advance the development of clinical tools that measure neurobehavioral tasks.

Boehringer Ingelheim, Janssen, Lundbeck and Roche are participating in the Reward Task Optimization Consortium (RTOC), along with central nervous system experts from medical and mental health institutions in the Netherlands, Germany, Spain and Greece. BlackThorn Therapeutics, a clinical-stage neurobehavioral health company, will provide next-generation AI solutions to help build predictive models.

RTOC, which will be led by central nervous system research company P1vital, will develop three computerized tools that measure brain activity in trial participants and then test the tools in trials for schizophrenia and major depression therapies. RTOC expects to start recruiting participants in Europe in the third quarter of 2019.

“Invisible” Device Uses Radio Signals to Analyze Movement and Collect Patient Data

Novartis and MIT are collaborating on development of a wireless device that can measure physical activity in patients without requiring them to use wearable sensors or monitors.

The “invisible” device analyzes surrounding radio signals, using machine learning algorithms to detect the pose and movement of a person, even through walls and in low light. It extracts various physiological metrics related to breathing, sleep stages, sleep apnea, mobility and gait, among others.

The “invisible” device provides several benefits over traditional patient data collection methods, including improved biomarker development and the ability to detect changes in behavior. And it allows patients to go about their normal routines without any added burden, which provides a unique opportunity to support at-home clinical trials.
**Up and Coming**

*This feature highlights changes in clinical research organizations’ personnel.*

**Vertex**
Vertex Pharmaceuticals has announced Reshma Kewalramani will assume the role of chief executive officer, effective April 1, 2020, when current CEO Jeffry Leiden transitions to the role of executive chairman of the board. Kewalramani currently serves as chief medical officer, a position she has held since 2017. In addition to CMO, she also serves as executive vice president of global medicines development and medical affairs. Kewalramani will become the first woman to run a large biotechnology firm.

**Astellas**
Chelsea Glinski has been appointed vice president, oncology sales at Astellas U.S. Glinski previously served as executive director of Astellas’ market access and reimbursement strategy.

**Healx**
Healx has named Neil Thompson chief scientific officer. Thompson previously served as senior vice president at Astex Pharmaceuticals.

**Noven Pharmaceuticals**
Noven Pharmaceuticals has announced the appointment of Andrew Purcell as head of marketing and sales. Purcell was previously vice president and head of the U.S. diabetes business unit for Sanofi.

**Ablative Solutions**
Kate Rumrill has been named president and chief executive officer at Ablative Solutions. Rumrill most recently served as president and CEO of NeoSync.

**Athira Pharma**
Athira Pharma has named Mark Litton as chief operating officer. Litton most recently served as chief business officer at Alder Biopharmaceuticals.

**Titan Medical**
Chad Zaring has been named chief commercial officer at Titan Medical. Zaring was most recently vice president of robotics, imaging and navigation at Medtronic.

**GlobalMed**
GlobalMed has named Robert Rennie as vice president, Europe, Middle East and Africa (EMEA). Rennie most recently served as vice president of EMEA for Atomiton.

**Gritstone Oncology**
Gritstone Oncology has named Vijay Yabannavar executive vice president of manufacturing and technical operations. Yabannavar was previously vice president of global technical operations at Merck.

**Selecta**
Massachusetts-based Selecta Biosciences has appointed Alison Schecter as chief medical officer. Schecter was formerly the global acting head of rare diseases and was responsible for leading the Niemann-Pick Disease (ASMD) project at Sanofi.

**Navitor Pharmaceuticals**
Randy Owen has been named chief medical officer at Navitor Pharmaceuticals. Owen most recently served as CMO at Acadia Pharmaceuticals.

**Selvita**
Krakow, Poland-based Selvita, S.A. has named Setareh Shamsili chief medical officer. Shamsili was previously interim CMO at Aximmune.

**Aurinia Pharmaceuticals**
Max Donley has been promoted to executive vice president of internal operations and strategy, and Glenn Schulman to senior vice president of corporate communications and investor relations at Aurinia Pharmaceuticals. Donley most recently led human resources, information technology and facilities at Senseonics. Schulman previously led corporate communications and investor relations at Achillion Pharmaceuticals.

**OncoCell MDx**
Michigan-based OncoCell has named Kirk Wojno as chief medical officer. Wojno was formerly the chief of pathology and laboratory services and director of clinical research at Comprehensive Urology.

**Karus Therapeutics**
Hilary McElwaine-John has been appointed chief medical officer at U.K.-based Karus Therapeutics. McElwaine-John was previously CMO at cancer gene therapy company PsiOxus.

**Immusoft**
Robert Hayes has been named chief scientific officer at Immusoft. Hayes, the former head of biologics at Amgen, was most recently CSO at Phyllogica.

**GlaxoSmithKline**
GlaxoSmithKline has announced the appointment of Kim Branson as senior vice president, global head of AI and machine learning. Branson was previously head of AI at Genentech.

**Pandion Therapeutics**
Pandion Therapeutics has announced that Rahul Kakkar has been named chief executive officer. Kakkar most recently served as the founding executive of Corvidia Therapeutics.

**Escient Pharmaceuticals**
Escient Pharmaceuticals has named Kristin Taylor as vice president and head of clinical development. Taylor most recently held the same role and helped lead efforts on therapies for Type 2 diabetes and obesity at Zafgen.

**AgilVax**
Joseph Patti has been named president and chief executive officer at AgilVax. Patti was most recently president of JP Biotech Advisors.
Real-World Trial
continued from page 1

seemingly simple study can have. “The
simpler we make the concept,” she says, “the
more complicated it is behind the scenes
and the longer it takes to get one of these
studies actually started.”

“I think this study took four years of dis-
cussion and planning before we hit the first
subject to be recruited.” The sheer numbers
of stakeholders in the asthma study alone
— 74 physician practices, 132 community
pharmacies, 165 trainers and facilitators
and 4,233 patients — meant determining
everyone’s needs was heavy lifting.

But buy-in is essential, Irving says. “These
types of studies can’t be done unless you
have a partnership with all the different par-
ties.” For the SLS, this meant reaching into
corners of the community in Salford and
South Manchester, England, to gather local
hospitals, primary care doctors, academic
experts and health informatics specialists.
In addition, SLS coordinators kept national
regulators up to date.

And keeping eligibility standards broad
resulted in a more representative study
population. Instead of employing tradition-
ally rigid clinical trial inclusion criteria, the
SLS tried to reach out to everyone in the
community with asthma and COPD, even
smokers and people with other comorbid
conditions.

In the COPD study, 11,720 patients reg-
istered to participate at their local doctor’s
office, 5,658 were found to be eligible, and
2,802 — 50 percent — were enrolled, a far
cry from the 841 patients who would have
qualified under more traditional clinical trial
standards.

Support for the physicians involved also
was a key factor. Trial designers wanted to
place as little burden on them as possible.
“If we had the design right,” Irving says, “we
were asking [them] to do their jobs. We
weren’t asking much else.” The SLS provided
nurse support teams to take on extra tasks
related to the trial, such as identifying
patients, conducting study visits and data
entry.

Training also was a necessary compo-
nent. These were research-naïve medical
professionals, Irving points out, who needed
education in good clinical practices and trial
procedures. Local pharmacies also needed
training in handling investigational drugs
and good manufacturing practices.

It was also important to make the study
team as diverse as possible, Irving says, com-
bining clinical statisticians used to working
only with eCRF data with epidemiologists
who specialize in real-world practice. “That
involves bringing two completely different
worlds together,” she says.

Using real-world data also requires a
change in mindset, Irving stresses. Data was
collected from patients only when it didn’t in-
terfere with their regular care, and then only
when the data added value to the study.

Outcomes and safety data were col-
lected from the electronic record systems
at general practices and pharmacies. That
presented a challenge all its own, according
to Martin Gibson, University of Manchester
professor and head of the team that created
the technology behind the study.

When it comes to electronic data records,
“standards are like toothbrushes — every-
one’s got one, but nobody wants to share,”
Gibson says. And varied data sources in an
RWD study make standardizing difficult.
They may have different coding systems,
data may be duplicated, sources may be
difficult to query.

In a real-world study, it’s necessary to
either build or buy “a system that brings all
those different data standards together,” he
says.

The outcome of GSK’s efforts ultimately
was positive. The SLS demonstrated not only
that Relvar was safe and effective, but also
that it improved patient outcomes in a real-
world setting, a factor that may strengthen
the drug’s position among payers.
Easy Document Access
continued from page 1

plan and a written strategy for processing inspection requests. It’s helpful, he says, to create a document matrix that shows the assigned document owners for each type of record likely to be requested.

For clues on what documents the FDA is likely to request, consult the FDA’s Compliance Program 7348.810, which provides agency personnel with instructions for conducting inspections.

“The challenge,” Chesney says, “is to meet the FDA requests in a timely and complete manner.” To evaluate your ability to do that, he suggests asking the following 10 questions:

1. Do your archives contain everything that may be requested during an inspection?
2. Are file names clear (ideally self-explanatory)?
3. Are there written requirements for in-house, remote or contracted employees and third-party vendors to transfer materials into the archives?
4. Do the archives contain more than one original and, if so, how are they differentiated?
5. Do the archives contain draft documents and, if so, how are they differentiated from final versions?
6. If archiving has been contracted to a third party, does the contract allow for prompt access for the records owner?
7. Are records produced by other parties for your company readily accessible (for example, CROs, contractors, consultants)?
8. Can documents be retrieved in a prompt and effective manner?
9. Have the access security measures associated with the archives been tested?
10. Do personnel responsible for the archives have the access and resources needed to produce documents during an inspection?

Chesney recommends testing document retrieval capabilities during mock inspections and internal audits, tracking how long it takes to properly fulfill a document request and working to improve that response time.

Finally, make sure to assign and train personnel who have first-hand knowledge of the documents to explain them during an inspection.


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<td>Ascentage Pharma</td>
<td>APG-2575</td>
<td>hematologic malignancies</td>
<td>Phase 1 trial initiated enrolling subjects with acute myelogenous leukemia (AML) and non-Hodgkin’s lymphoma (NHL) in China</td>
<td>ascentagepharma.com</td>
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<td>Halozyme Therapeutics</td>
<td>efgartigimod (ARGX-113)</td>
<td>severe autoimmune diseases</td>
<td>Phase 1 trial initiated</td>
<td>halozyme.com</td>
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<td>AC Immune SA</td>
<td>ACI-3024</td>
<td>neurodegenerative diseases that are characterized by the presence of pathological Tau aggregates</td>
<td>Phase 1 trial initiated enrolling healthy volunteers</td>
<td>acimmune.com</td>
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<tr>
<td>NuCana plc</td>
<td>NUC-7738</td>
<td>cancer</td>
<td>Phase 1 trial initiated</td>
<td>nucana.com</td>
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<td>CStone Pharmaceuticals</td>
<td>ivosidenib (TIBSOVO)</td>
<td>relapsed or refractory acute myeloid leukemia (R/R AML) with an IDH1 mutation</td>
<td>Phase 1 trial initiated</td>
<td>cstonepharma.com/en/</td>
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<td>Prescient Therapeutics Ltd.</td>
<td>PTX-100</td>
<td>cancer</td>
<td>Phase 1b trial initiated enrolling subjects in Australia</td>
<td>ptxtherapeutics.com</td>
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<td>Axial Biotherapeutics</td>
<td>AB-2004</td>
<td>gastrointestinal dysfunction and associated behavioral symptoms of Autism Spectrum Disorder (ASD)</td>
<td>Phase 1b/2a trial initiated enrolling 25 male subjects with ASD</td>
<td>axialbiotherapeutics.com</td>
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<tr>
<td>ImaginAb Inc.</td>
<td>CD8 tracer 89Zr-Df-IAB22M2C</td>
<td>cancer</td>
<td>Phase 2 trial initiated enrolling subjects at Dana-Farber Cancer Institute in Boston</td>
<td>imaginab.com</td>
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<tr>
<td>DelMar Pharmaceuticals, Inc.</td>
<td>VAL-083</td>
<td>MGMT-unmethylated glioblastoma multiforme (GBM)</td>
<td>Phase 2 trial initiated enrolling 24 newly-diagnosed subjects who have undergone surgery and chemoradiation with temozolomide (TMZ) at the University of Texas MD Anderson Cancer Center (MDACC)</td>
<td>delmarpharma.com</td>
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<tr>
<td>EIP Pharma, Inc.</td>
<td>neflamapimod</td>
<td>cognitive dysfunction associated with dementia with Lewy bodies (DLB)</td>
<td>Phase 2 trial initiated enrolling 80 subjects at several sites in the U.S. and Netherlands</td>
<td>eippharma.com</td>
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<tr>
<td>Oyster Point Pharma, Inc.</td>
<td>OC-01 Nasal Spray</td>
<td>dry eye disease</td>
<td>Phase 3 trial initiated enrolling 750 subjects at 20 centers in the U.S.</td>
<td>oysterpointinx.com</td>
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<td>LifeMax Laboratories, Inc.</td>
<td>LM-030</td>
<td>Netherton Syndrome</td>
<td>Rare Pediatric Disease designation granted by the FDA</td>
<td>lifemaxlabs.com</td>
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<tr>
<td>Merck and Eisai</td>
<td>KEYTRUDA in combination with LENVIMA</td>
<td>subjects with advanced unresectable hepatocellular carcinoma (HCC) not amenable to locoregional treatment</td>
<td>Breakthrough Therapy designation granted by the FDA</td>
<td>merck.com eisai.com</td>
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## Drug & Device Pipeline News

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<td>LivaNova PLC</td>
<td>LifeSPARC</td>
<td>cardiac and respiratory failure</td>
<td>510(k) clearance granted by the FDA</td>
<td>livanova.com</td>
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<td>Advanced Circulatory Support (ACS) system</td>
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<td>Aridis Pharmaceuticals, Inc.</td>
<td>AR-501</td>
<td>cystic fibrosis</td>
<td>Orphan Drug designation granted by the FDA</td>
<td>aridispharma.com</td>
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<td>Arrowhead Pharmaceuticals Inc.</td>
<td>ARO-ANG3</td>
<td>homozygous familial hypercholesterolemia (HoFH)</td>
<td>Orphan Drug designation granted by the FDA</td>
<td>arrowheadpharma.com</td>
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<td>Apic Bio, Inc.</td>
<td>APB-102</td>
<td>genetic SOD1 amyotrophic lateral sclerosis (ALS)</td>
<td>Orphan Drug designation granted by the FDA</td>
<td>apic-bio.com</td>
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<td>Teva Pharmaceuticals Industries Ltd.</td>
<td>AirDuo Digihaler</td>
<td>asthma</td>
<td>Approval granted by the FDA</td>
<td>tevapharm.com</td>
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<td></td>
<td>(fluticasone propionate 113 mcg and salmeterol 14 mcg) Inhalation Powder</td>
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<td>Novadoz Pharmaceuticals</td>
<td>Abiraterone Acetate 250mg tablet</td>
<td>prostate cancer when used with a steroid medication (prednisone or methylprednisolone)</td>
<td>Approval granted by the FDA</td>
<td>novadozpharma.com</td>
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<td>Bayer</td>
<td>Gadavist (gadobutrol) injection</td>
<td>coronary artery disease (CAD)</td>
<td>Approval granted by the FDA</td>
<td>bayer.com</td>
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<td>Abbott</td>
<td>MitraClip heart valve repair device</td>
<td>mitral regurgitation</td>
<td>Approval granted by the FDA</td>
<td>abbott.com</td>
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<td>Merck</td>
<td>RECARBRIO (imipenem, cilastatin and relebactam) for injection (1.25 grams)</td>
<td>adults with complicated urinary tract and complicated intra-abdominal bacterial infections where limited or no alternative treatment options are available</td>
<td>Approval granted by the FDA</td>
<td>merck.com</td>
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<td>Celgene</td>
<td>OTEZLA (apremilast)</td>
<td>adult with oral ulcers associated with Behçet's Disease</td>
<td>Approval granted by the FDA</td>
<td>celgene.com</td>
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<td>Baxter</td>
<td>Myxredlin</td>
<td>ready-to-use insulin for IV infusion</td>
<td>Approval granted by the FDA</td>
<td>baxter.com</td>
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<td>Pfizer, Inc.</td>
<td>RUXIENCE (rituximab-pvvr)</td>
<td>adult subjects with non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL) and granulomatosis with polyangitis (GPA) and microscopic polyangiitis (MPA)</td>
<td>Approval granted by the FDA</td>
<td>pfizer.com</td>
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<tr>
<td>Samsung Bioepis Co., Ltd.</td>
<td>HADLIMA (adalimumab-bwwd)</td>
<td>rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis and plaque psoriasis</td>
<td>Approval granted by the FDA</td>
<td>samsungbioepis.com</td>
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<tr>
<td>Eli Lilly and Company</td>
<td>Baqsimi (glucagon) nasal powder 3 mg</td>
<td>severe hypoglycemia</td>
<td>Approval granted by the FDA</td>
<td>lilly.com</td>
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